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RESEARCH PAPER

HYPOGLYCAEMIC AND HYPOLIPIDEMIC EFFECTS OF THE PHYTOMEDICINE - BEE HONEY AND *MUSA PARADISIACA* EXTRACT - IN ALLOXAN-INDUCED DIABETIC RATS

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ABSTRACT

This study examines the safety, hypoglycaemic and hypolipidemic effects of a phytomedicine – a mixture of bee honey *and Musa paradisiaca* roots extract. Toxicity was evaluated in Swiss albino mice using graded oral doses of the drug (1.0g to 20.0g /kg body weight) and observed continuously; first for 4hrs, hourly for the next 24hrs, then 6-hourly for 48hrs. Diabetes was induced in groups 1, 2 and 3, using intraperitoneally administered solution of alloxan monohydrate in normal saline (150 mg/kg b.wt). Groups 1 and 2 were respectively treated with a reference drug – glibenclamide, and the extract (250mg/kg b.wt) continuously for 30 days. The effects on plasma glucose and some biochemical parameters were evaluated at the end of the experiment as indices for antidiabetic activity. The observed median acute toxicity value (LD_{50}) of the drug was 18.84g/Kg b.wt. There were significant reductions ($p<0.05$) in plasma glucose and low density lipoprotein levels, and significant increase ($p<0.05$) in high density lipoprotein in the treated diabetic group compared to the control. The results showed that the phytomedicine had both good hypoglycemic activity and good effects on cardiovascular risk factors and the high LD_{50} value is an indication that the drug has a high margin of safety.

***Keywords:* Musa paradisiaca, bee honey, acute-toxicity, diabetes**

INTRODUCTION

Diabetes in recent times has become one of the devastating diseases and is accounting for a high proportion of health problems worldwide (Sushruta et al., 2006). It is now recognized as one of the leading causes of death among the influential in the developing countries, where the high prevalence of the disease can be attributed to improved nutritional status coupled with a gross lack of modern facilities for the early diagnosis of the disease (Ogbonnia et al., 2008). Diabetes mellitus has been described as the common metabolic disorder of carbohydrate and fat metabolism, which is due to absolute or relative lack of insulin and is characterized by hyperglycaemia (Walter, 1977, Tierney et al., 2002). It is succinctly put by Barnett and O'Gara (2003), as "a state of premature cardiovascular death that is associated with chronic hyperglycemia, and may be associated with blindness and renal failure." Diabetes is commonly accompanied by other cardiovascular risk factors such as dyslipidemia, hypertension, prothrombic factors and microvascular problems involving eyes, kidney and peripheral nerves (Grundy et al., 1999, Barnett and O'Gara, 2003).

Two main types of diabetes based on their clinical manifestations are identified' type I diabetes known as juvenile onset or insulin sensitive diabetes and type II diabetes or non insulin dependent diabetes mellitus (NIDDM), and is the most prevalent form. Type II diabetes may have as its underlying metabolic causes the combined effects of

impairment in the insulin-mediated glucose disposal and defective secretion of insulin by the β-cells of the pancreas (Pari and Saravanan, 2004).

Oral hypoglycaemic agents especially the sulphonylureas and biguanides have been commonly employed in the treatment and management of type II diabetes (El Naggar et al., 2005). Sulphonylureas are the most widely used oral hypoglycaemic agents but may have some adverse effects such as exacerbating hyperinsulinaemia, thereby causing weight gain in patients (Egwim, 2005; Rastogi et al., 1997). The use of sulphonylureas is restricted by their pharmacokinetic properties, secondary failure rates and accompanied side effects while biguanides are only weak hypoglycaemics and have limited clinical use (El Naggar et al., 2005; Pari and Saravanan, 2004). For these cogent reasons therefore, there is a great need for a search for an acceptable, cheap and safe blood sugar lowering oral hypoglycaemic agent that would be effective in the treatment of diabetes and devoid of serious side effects of the currently used oral hypoglycaemic agents.

Herbs and marine sources have been considered the best option (Ogbonnia et al., 2010). The use of herbal preparations and natural products from various plant sources in the management of diabetes mellitus is now of great interest and is an area where a lot of research is in progress. Several herbs have been reported in the folk medicine to be successfully employed in the management of diabetes and have shown effectiveness in non-insulin dependent diabetes-type II diabetes (Shah Ayub et al., 1997).

The phytomedicine – a mixture of bee honey and *Musa paradisiaca* roots extract - is one of such preparations used in Nigerian folk medicine to treat diabetes. Bee honey is a sweet yellow to rich amber colored viscous fluid that has been recognized for its food and various medicinal values. It has been evaluated for antibacterial effects in wound healing (Fakoor and Pipelzadeh, 2007; Jeffrey and Echazarreta, 1996; Armstrong and Otis, 1995). Studies have shown that a 20% solution of honey inhibits *Helicobacter pylori* organisms, one of the causative agents of gastritis (Jeffrey and Echazarreta, 1996). Pure honey has been shown to have bactericidal activity against many enteropathogenic organisms including those of the *Salmonella* and *Shigella* species and *E. coli* (Jeddar et al., 1985). Also chemical analyses have revealed that honey possess surprising quantities of antioxidants, non-nutritive agents that can retard biologically destructive chemical reactions that cause rancidity in food and have been linked up to counter many chronic diseases (Llesuy et al., 2001; Gomez et al., 1998). Different parts of *Musa paradisiaca* plant is either used alone or in combination with other herbal products by herbalists in the management of diabetes and other diseases.

The aim of this study was to carry out the acute toxicity of the phytomedicine in mice and also evaluate the effects of the drug on plasma glucose levels, and on some cardiovascular risk factors, body weight and renal toxicity, following its oral administration in alloxan-induced diabetic rats.

MATERIALS AND METHODS

Materials: The phytomedicine - bee honey and *M paradisiaca* extract - was ceded by a traditional practitioner, Mr. Agu T.I. of No 105, Itire - Mushin Road, Itire, Lagos, Nigeria.

Composition of the phytomedicine

M. paradisiaca lyophilized extract	22.5g
Bee Honey	20ml
Purified water (qs)	100ml

The phytomedicine is a clear and slightly thick brown liquid stored in an amber glass bottle of 600ml.The prescribed dose for human is equivalent to three table spoon (30ml) three times a day. Five hundred milliliters (500ml) of the phytomedicine was filtered through a muslin cloth and lyophilized to give 47.65g gel.

Animals: Swiss mice (20 - 25g) and Wistar rats (160±20g) of both sexes were obtained from the Laboratory Animal Center, College of Medicine, University of Lagos, Idi-Araba and were kept under standard environmental condition of 12/12hr light/dark cycle.

They were housed in cages (5 animals per cage), maintained on animal cubes (Feeds Nigeria Ltd), and provided with water *ad libitum.* They were allowed to acclimatize for seven days to the laboratory conditions before the experiment.

Acute toxicity study: The toxicity study was carried out using thirty- five (35) male and female Swiss albino mice. The animals were randomly distributed into a control group and six treated groups, containing five animals per group. After depriving them food overnight, the control group received 0.3ml of normal saline orally while each treated group received orally solution of the gel in normal saline in the doses of 1.0, 2.5, 5.0, 10.0, 15.0 and 20.0g /kg body weight respectively.

They were observed continuously for the first 4 hours and then for each hour the next 24 hours and at 6 hourly interval for the next 48 hours after administering the drug to observe any death or changes in general behavior and other physiological activities (Bürger et al., 2005; Mahdi et al., 2003).

Diabetic study: adult Wistar rats of both sexes weighing 160g±20g were used. The animals were fed on animal cubes (Feeds Nigeria Ltd) and provided with water *ad libitium*. Diabetes was experimentally induced after fasting the animals overnight by administering intraperitoneally (i.p.) alloxan monohydrate dissolved in normal saline (150mg/kg) (Mbaka et al., 2008).

After 72 hours, the blood sugar levels were monitored with a glucometer (*Accu-Chek*, Roche Diagnostics) and the rats with plasma glucose level >200mg/dl were classified as diabetic (Ogbonnia et al.,2011) and were included in the study. A total of five groups containing five animals per group were used. Three groups were diabetic while the remaining two groups were used as different controls and were treated daily for 30days as follows:

Group I: Induced diabetic rats treated daily with Glibenclamide 600µg/kg b. wt (Wasan et al., 2001),
Group II: Induced diabetic rats treated daily with the drug 250mg / kg body weight (b.wt)
Group III: Induced diabetic rats but not treated
Group IV: Normal rats treated daily with the drug 250mg/kg b. wt
Group V: Control given 0.5ml normal saline daily

The animals were initially weighed and then weighed every five days from the starting of the treatment. On the 31st day, they were made unconscious by cervical dislocation and blood obtained via cardiac puncture into heparinized and EDTA containers for biochemical and blood chemistry studies respectively.

Sample analysis: The heparinized blood was centrifuged within 5 min of collection at 4000g for 10min to obtain plasma, which was analyzed for glucose level, total cholesterol, total triglyceride, HDL-cholesterol levels by precipitation and modified enzymatic procedures from Sigma Diagnostics (Crook, 2006). LDL-cholesterol levels were calculated using Friedwald equation (Hussain and Eshrat, 2002). Plasma was analyzed for alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatinine by standard enzymatic assay analysis. The plasma protein contents and plasma glucose contents were determined using enzymatic spectroscopic methods (Ghosh, 1984).

Statistical Analysis: Analysis of Data was done using Statistical Package for Social Sciences version 16.0. One way analysis of variance and t-test were used to compare means. Means ± SEM are shown in all tables. Level of significance was set at $p<0.05$ or $p<0.01$.

RESULTS

In the acute toxicity study (Table I), three out of the five animals that received 20.0g/kg b.wt of the extract died within 4hr (60% death) while the animals that received 10g/kg b.wt survived beyond 24hr. LD_{50} of the drug was calculated to be 18.84g/kg b.wt. The effect of the phytomedicine on the body weights of the diabetic and normo-rats and also the effect of the reference drug, glibenclamide, on the diabetic rats are shown in Table II. There was a significant increase ($p<0.05$) in weight of the diabetic animals (group I) treated with glibenclamide. There were significant increase in body weights of the diabetic and normal rats treated with the drug (groups II and IV respectively) compared with the diabetic control. However, a significant decrease in weight in the non-treated diabetic group compared with the control was observed (Figure I).

The results of the effects of the drug and glibenclamide on the organs of the diabetic animals and on the normo-rats were presented in Table III. The macroscopic examinations of the organs of the animals treated with the drug and glibenclamide did not show any changes in colour while the organs of untreated diabetic animals showed some changes compared with the control. Table IV summarized the results of the phytomedicine and glibenclamide effects on the biochemical parameters. The plasma glucose level of the diabetic rats treated with the drug and

glibenclamide were significantly reduced ($p<0.05$) compared with the control. There was an astronomical increase in the plasma glucose level of the alloxan-induced but untreated animals compared with the control, showing they were truly diabetic.

There was a significant increase ($p<0.05$) in the plasma AST and ALT levels in the untreated diabetic animals compared with the control while a significant decrease ($p<0.01$) in AST and ALT levels were observed in the diabetic animals treated with the drug compared with the control. A significant decrease ($p<0.05$) in the plasma total cholesterol (TC) level was observed in the diabetic animals treated with the drug compared with control while a significant increase in TC level was observed in untreated diabetic rats compared with control.

There was also a significant decrease ($p<0.05$) in both triglyceride (TG) and LDL-cholesterol levels in diabetic animals treated with the drug compared with the control while significant increase in HDL-cholesterol levels were observed in all diabetic animals treated with the drug or glibenclamide compared with the control. The untreated diabetic animals showed a significant increase in both TG and LDL-cholesterol levels compared with control and a significant decrease in HDL-cholesterol levels compared with control.

There was a significant increase in the plasma protein levels of the diabetic animals treated with the drug and glibenclamide compared with control, while a significant increase was observed in the creatinine levels of the untreated diabetic animals compared with control.

Table I: Acute toxicity of the phytomedicine - bee honey and *M.paradisiaca* roots - in mice

Doses of Drug gel g/kg	Number of mice used	Number of mice dead	% Cumulative mice dead
0	5	0	0
1.0	5	0	0
2.5	5	0	0
5.0	5	0	0
10.0	5	0	0
15.0	5	1	25
20.0	5	3	100

Control group received 0.3ml each of normal saline

Table II: Weight variation of the control, untreated diabetic rats, diabetic rats and normal rats treated with the phytomedicine and diabetic rats treated with glibenclamide doses for 30 days

Group	DAY 1	DAY 5	DAY 10	DAY 15	DAY 20	DAY 25	DAY30
I	154.3±6.70	158.6 ± 6.7	159.01± 0.4	161.02±0.1	162.05±0.2	164.7±8.8	165.6±8.3*
II	150.4 ±1.30	151.3 ± 1.1	156.40 ± 1.2	160.6 ± 1.7	163.41 ± 1.2	165.3 ± 1.2	170.5 ± 2.5*
III	180.3±2.50	175.2 ± 1.50*	169.20.±3.3	166.7± 2.8*	162.2 ± 2.8	156.6±2.2*	154.5±1.3*
IV	174.5±2.50	174.92±1.07	179.03±0.3	181.20± 1.2	186.51±1.4*	189.20±1.0*	193.6± 0.2*
V	173.7±2.60	174.20 ± 2.3	75.02±2.9	77.20 ± 2.2	179.70±2.2	181.25.±1.7	183.01±17

Mean ± sem, (n=5) *p<0.05; ** p<0.01 vs control group. Control group received 0.5ml normal saline. Group I: diabetic rats treated with Glibenclamide 600µg b.wt; Group II: diabetic rats treated with 250mg extract/kg wt, Group III: diabetic rats without treatment. Group IV: normal rats treated 250mg extract /kg wt. Group V Control rats received 0.5ml normal saline

DISCUSSION

The median acute toxicity value (LD_{50}) of the lyophilized drug preparation was determined to be 18.84g /kg body weight. According to Ghosh (1984) and Klaasen et al. (1995) the phytomedicine can be classified as being non-toxic, since the LD_{50} was found to be over 15g/kg. The viscera of the dead animals did not show any macroscopic changes that could point to the cause of the death. Since the animals did not convulse before dying, it could be inferred that the phytomedicine did not kill the mice by some action on the nervous system (Ogwal-Okeng et al., 2003).

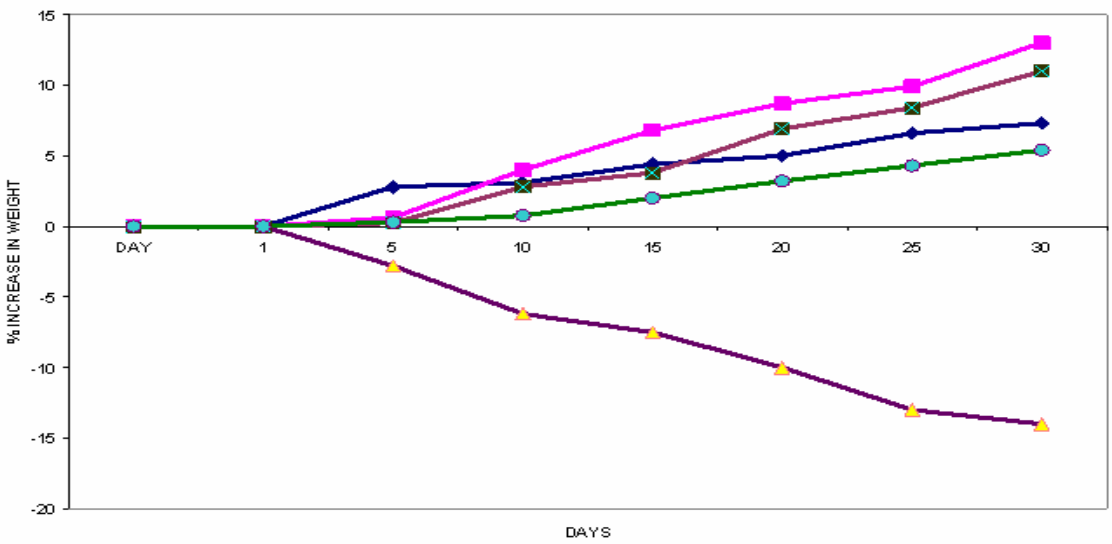

Fig.I. Percentage increase in weight of untreated diabetic animals, diabetic treated with the phytomedicine and glibenclamide respectively and normorats treated with phytomedicine

(Keys =♦Group I diabetic rat treated with glibenclamide, ■ GroupII diabetic rat treated with phytomedicine, ▲Group III untreated diabetic rat, x Group IV normorat treated with the phytomedicine and ●Group V normorat treated with 0.5ml normal saline)

Table III: The effects of the extract and glibenclamide on kidney, heart, liver and brain of the diabetic rats, and also the effect of the extract on normal rats compared with the control

Organ	Group I	Group II	Group III	Group IV	Group V
Heart (g)	0.69 ± 0.03	0.51 ± 0.23	0.68 ± 0.13	0.72 ± 0.06	0.69 ± 0.23
Kidney (g)	0.93 ± 0.10	0.77± 0.18	1.31±0.06	0.9 ±0.06	1.02± 0.24
Liver (g)	3.097 ± 0.70	2.80± 0.53	5.14±0.57*	4.10 ±0.63*	3.00 ± 0.43
Brain (g)	1.168 ± 0.14	1.07 ± 0.01*	1.09 ± 0.01	1.11 ± 0.07	1.37 ± 0.02

Mean ± sem, (n=5) *p<0.05; ** p<0.01 vs control group. Control group received 0.5mL normal saline. Group I: diabetic rats treated with Glibenclamide 600µg b.wt; Group II: diabetic rats treated with 250mg extract/kg wt; Group III: diabetic rats without treatment. Group IV: normal rats treated 250mg extract /kg wt. Group V Control rats received 0.5ml normal saline

Table IV: Plasma glucose level and other biochemical profiles of untreated diabetic rats, diabetic but treated with the extract and glibenclamide respectively and the normal rats treated with extract and the control

Parameter	Group I	Group II	Group III	Group IV	Group V
Glucose (mg/dl)	108.03±0.60*	109.75±20.10*	312.00±1.20	75.95±0.50*	112.60±2.45
Cholesterol (mg/dl)	172.46±2.10	143.15±5.20*	684.23±1.60*	116.12±3.10	173.65±0.54
Triglyceride (mg/dl)	161.87±0.80	23.4±3.60*	288.26±0.72*	95.57±1.50	113.81±2.10
HDL (mg/dl)	303.32±1.60 *	143.46±2.90*	3.25±2.2*	471.52±0.60	48.56±4.10
LDL (mg/dl)	5.30±2.60	2.52±7.40*	76.85±0.60 *	8.83±1.50	6.44±2.20
Protein (g/dl)	6.65±0.45*	5.20±0.05 *	2.80±0.20	7.82± 0.72	3.12±0.25
Creatinine (mg/dl)	0.19±0.002	0.34±0.23	13.33±0.06*	0.58± 0.02	0.69±0.52
AST (I.U/L)	12.18±1.20	12.04±2.1**	55.69±2.50*	8.14± 0.02	18.83±0.90
ALT (I.U/L)	76.56±1.50	17.80±4.52 **	47.60±2.75*	14.74± 3.53	23.30±1.32

Mean ± sem, (n=5) *p<0.05; ** p<0.01 vs control group. Control group received 0.5mL normal saline. Group I: diabetic rats treated with Glibenclamide 600µg b.wt, Group II: diabetic rats treated with 250mg drug/kg wt, Group III: diabetic rats without treatment. Group IV: normal rats treated 250mg extract /kg wt. Group V Control rats received 0.5mL normal saline

Table V. Effect of the drug on haematological parameters of the control and treated animals in the subchronic toxicity study

Parameter	Group I	Group II	Group III	Group IV	Group V
RBC (10^6 /mm^3)	3.67±0.04	3.85±0.06	5.28±0.05*	6.19±0.06*	6.52± 0.60
WBC (10^3 /mm^3)	4.30±0.03	10.85±1.65*	9.90±0.02	2.08±0.02*	4.41± 0.50
PCV (%)	32.0± 2.20	33.05± 1.52	26.85± 2.50*	40.55± 0.50	32.79± 0.10
Calcium (mg/dl)	10.03±0.04	9.72± 0.05	11.58± 0.04*	8.24± 0.03	9.26± 0.20
Phosphorus (mg/dl)	3.99± 0.03	3.40 ± 0.95	3.00± 0.001	2.75± 0.04	3.06± 0.40

Mean ± SEM (n = 5),*p<0.05; ** p<0.01 vs. control group. Control group received 0.5mL normal saline solution. Group I: diabetic rats treated with Glibenclamide 600µg b.wt; Group II: diabetic rats treated with 250mg drug/kg wt, Group III: diabetic rats without treatment. Group IV: normal rats treated 250mg extract /kg wt. Group V Control rats received 0.5ml normal saline

The treatment with the drug did not decrease the water and food consumption by the animals. Treatment of the diabetic and normal rats with the drug however produced significant changes in the body weights of the animals. Also the diabetic animals treated with glibenclamide showed a significant gain in weight. The increase in the weight of the diabetic animals treated with the drug, therefore, clearly demonstrated that the drug might not lack the obesity forming tendency, which is one of the serious side effects normally encountered when treating diabetics with sulphonylureas. There were no changes observed in the macroscopic examinations of the organs of the diabetic animals treated with the drug or glibenclamide.

The drug had a remarkable effect on the plasma glucose levels especially on the diabetic rats and proved to have a good plasma glucose lowering effects. Low blood glucose level reduces the risk of complications associated with diabetes. This finding gives support to the use of the drug preparation as a hypoglycaemic agent. The liver releases alanine aminotransferase (ALT) and an elevation in the plasma concentration is an indicator of liver damage. The liver and heart release aspartate aminotransferase (AST) and ALT, and an elevation in their plasma concentrations is an indicator of liver and heart damage (Crook, 2006). The decrease in the ALT and AST levels in the diabetic animals treated with the phytomedicine implied that the drug at the doses used, neither produced any harmful effects on the heart tissues nor provoked some detrimental effects on liver tissues. The remarkable increase both in the plasma AST and ALT levels in the untreated diabetic animals was an indication of heart and liver problems which usually result from untreated diabetes.

The drug lowered plasma total cholesterol (TC) concentration, triglyceride (TG) and LDL-cholesterol levels while there was significant increase in HDL-cholesterol level in the treated animals were observed. This clearly demonstrates the presence hypolipidemic agents in the phytomedicine. The drug also had some beneficial effects on cardiovascular risk factors, which contribute to death in diabetic patient (Ceylan-Isik et al., 2008; Zhou et al., 2006; Valli and Giardina, 2002). This observation supported the local use of the seeds' preparation as a hypoglycaemic agent. The increase in plasma protein and decrease in creatinine levels of the diabetic animals treated with the drug compared to the control means that the renal function of the animals was not impaired. An increase in plasma creatinine levels coupled with decrease in the protein levels may be a sign of impaired renal function for the animals affected.

Conclusion

The high LD_{50} value (18.84g/kg) obtained was a clear indication that *M. paradisiaca* and Bee honey preparation is safe for use. The phytomedicine demonstrated a good hypoglycemic and hypolipidemic activity with desirable effects on cardiovascular risk factors. The study also revealed that the drug is not nephrotoxic nor hepatotoxic.

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AUTHORS' CONTRIBUTIONS

The experiment was conceived and designed by Emordi, E.J., Ogbonnia, O.S., Olayemi, O.S. Emordi, E.J., Ogbonnia, O.S., Olayemi, O.S., Anyika, N.E., Iribhogbe, I.O. performed the experiments. Emordi E.J. and Ogbonnia O.S. wrote the paper.